REMARKS

The present invention provides immunomodulating compositions for modulating an immune response comprising a nucleic acid construct encoding at least one epitope from a self-antigen and a compound selected from the group consisting of a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and combinations thereof, in a pharmaceutically acceptable carrier. The invention further provides methods for modifying an ongoing immune response in a subject against a self-antigen associated with autoimmune diabetes by administering to the subject by peripheral injection an immunomodulatory effective amount of a plasmid expressing a nucleic acid construct encoding at least one epitope from a self-antigen associated with autoimmune diabetes in a pharmaceutically acceptable carrier.

Transient expression of the epitope in the subject results in a positive regulatory immune response to multiple self-antigens associated with the autoimmune diabetes. In yet another embodiment, the invention provides methods for controlling the blood glucose level in a subject having an ongoing immune response against a self-antigen associated with autoimmune diabetes. In this embodiment, the subject is administered by peripheral injection, an immunomodulatory effective amount of a plasmid expressing a nucleic acid construct encoding at least one epitope from a self-antigen associated with autoimmune diabetes in a pharmaceutically acceptable carrier such that expression of the epitope in the subject results in a positive regulatory immune response against multiple self-antigens associated with the autoimmune diabetes. As a result, the blood glucose level of the subject is controlled.

Claims 1-36 were pending before this response (not 1-38 as shown in the cover sheet to the Advisory Action). By the present communication, claims 7, 13, 18, 23, 25, 26, and 28 are canceled without prejudice and claims 1-3, 6, 8, 9, 11, 15, 17, 19, 20, 22, 27, 29 and 32-36 are amended to define Applicant's invention with greater particularity. No new matter has been added as the new claim language is fully supported by the specification and original claims. Applicant submits that the claim amendments do not narrow the claims in any way within the meaning of Festo Corporation v. Shoketsu Kinzoku Kogyo Kabushiki Co. Ltd., a/k/a SMC Corporation and SMC Pneumatics, Inc., 234 F.3d 558, 51 U.S.P.Q. 2d 1959 (Fed. Cir. 2000).

Accordingly, claims 1-6, 8-12, 14-17, 19-22, 24, 27, and 29-39 are currently pending and under consideration as shown in attached Exhibit A.

The Specification

The Examiner has requested amendment of the Specification to show proper use of the trademarks, for example ACCUCHECK III and TWEEN. In compliance, the Specification has been amended by the present communication to provide proper use of the trademarks ACCUCHECK III and TWEEN.

The Rejection under 35 U.S.C. § 112, First Paragraph

Applicant respectfully traverses the rejection of claims 1-31 under 35 U.S.C. § 112, first paragraph, for alleged lack of an enabling disclosure. Applicant disagrees with the Examiner's assertion that the specification does not reasonably provide enablement for treatment of any autoimmune disorder, such as diabetes. In particular, Applicant disagrees with the Examiner's assertion that "Giannoukakis et al. have taught the unpredictability *of the claimed invention*" (Office Action, page 5, emphasis added). In fact, Giannoukakis' assertions regarding the safety risks and unpredictability pertain to therapeutic treatments of diabetes wherein foreign islet producing cells (for example, porcine cells or cell obtained from cadavers) are introduced into the subject, but do not, therefore, apply to the present invention. Giannoukakis' method of transplanting insulin producing cells depends for utility upon *in vivo* viability and continued function of transplanted cells in the subject's body (i.e., to produce a therapeutic amount of insulin). Because the cells are foreign, the subject's host inflammatory response tends to destroy the transplanted cells and may attack healthy islet cells as well.

Alternatively, in the embodiments of Giannoukakis' method wherein DNA is administered to a subject, the method utilizes a gene therapy-like application, wherein efficacy of the treatment requires that the gene product be expressed in the subject over an extended period of time and at substantial levels to supplement a lack of insulin. Thus, in all cases the treatment is successful only so long as the administered construct produces a therapeutic drug *in vivo* in the subject. Applicants respectfully submit that "no showing of any previous success" by

Giannoukakis, as asserted by the Examiner, does not necessarily predict constant lack of success in future scientific attempts, particularly when different methods and strategies are employed.

Applicant's methods and strategies differ considerably from those employed by Giannoukakis. In Applicant's methods for "modifying an ongoing immune response" (as required by amended claim 11) and for "controlling the blood glucose level in a subject having an ongoing immune response against a self-antigen associated with autoimmune diabetes" (as required by amended claim 22), the subject is administered *by peripheral injection* an immunomodulatory effective amount of a plasmid expressing a nucleic acid construct encoding at least one epitope from a self-antigen associated with autoimmune diabetes. The goal is to accomplish transient expression of the epitope in the subject resulting in a positive regulatory immune response to multiple self-antigens associated with the autoimmune diabetes. No porcine cells are required to be implanted into the subject, with all the attendant inherent risks of rejection described by Giannoukakis. In fact, in many cases Applicant's nucleic acid construct can encode a purely human product.

Efficacy in Applicant's invention methods requires only sufficient expression of the foreign protein to raise "a positive regulatory immune response." Thus the construct need function in the subject's body only long enough for the immune response to be triggered and booster doses may be administered, as needed, in accordance with routine practice. Studies have shown that expression by only hundreds to thousands of cells is sufficient for this purpose (See http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10837410&dopt=Abstract)) Continuous expression of the administered construct is not contemplated and would be counterproductive. So Giannoukakis' concerns about the subject's body rejecting foreign islet cells so as to cause immune destruction of healthy islet cells does not apply to the present invention.

Thus, Applicant submits that the Examiner's arguments concerning unpredictability and lack of enablement of the present invention in view of the warnings of Giannoukakis are not sufficient to support a rejection for lack of enablement under 35 U.S.C. 112, First Paragraph. Accordingly, Applicants request reconsideration and withdrawal of the rejection as applied to amended claims 1, 11 and 22.

In addition, Applicant respectfully submits that those of skill in the art could readily provide nucleic acid encoding an epitope of a self-antigen and a biological response modifier for a human subject that could be transiently transfected into a subject so as to generate "a positive regulatory immune response" in a subject to which it is administered. The Wands factors that might apply to the question of enablement of the experimental protocol disclosed by Giannoukakis are simply different that those that apply to Applicant's invention.

Given the level of knowledge in the art at the time the present application was filed, and the guidelines in the present application, Applicant submits that those of skill in the art would know how to prepare nucleic acid encoding an epitope of a self-antigen (especially a self-antigen known to be associated with the etiology of type 1 diabetes) and, optionally, a biological response modifier, that would be fully compatible with the subject to be treated, whether mouse or human, and which would raise a positive immune response in the subject. For example, Applicant discloses a number of different "expressed epitopes" useful for treating diabetes (Specification, page 34, lines 4-13). Additional epitopes are known in the art and will be discovered in the future. In addition, nucleic acid encoding fully human cytokines and chemokines was known at the filing date of the present invention (Specification, page 27, line 24 to page 28, line 16).

However, to reduce the issues and expedite prosecution, Applicant has amended the present method claims to recite modifying an ongoing immune response in a subject against a self-antigen associated with autoimmune diabetes (claim 11) or controlling the blood glucose level in a subject having an ongoing immune response against a self-antigen associated with autoimmune diabetes (claim 22). Those of skill in the art recognize that insulin and GAD are self-antigens in type 1 diabetes in humans and in spontaneous animal models.

In illustration of the invention constructs and methods, Applicant has utilized two complementary mouse models of autoimmune diabetes. In the first, the RIP-LCMV model, the disease is triggered by viral infection and mediated by molecular mimicry. Thus, this is an "environmental" model. The second model is a spontaneous disease model, the NOD mouse model, based on segregation of a number of diabetes-associated genes that predispose to disease irrespective of environmental factors. Since the human disease is triggered by an interplay of

genetic and environmental factors, these models represent the two mechanisms operative in human autoimmune diabetes. Applicant respectfully submits that a demonstration that plasmid-mediated expression of insulin B is effective in *both* models would be considered by those of skill in the art to be predictive for human outcomes. In support of this assertion, Applicant submits herewith two review articles published in peer reviewed scientific publications that specifically address the parallels between the mouse models and the mechanism of the human disorder: T.L. Delovitch et al. "The Nonobese Diabetic Mouse as a Model of Autoimmune Diabetes: Immune Dysregulation Gets the NOD," *Immunity* 7:707-736, 1997 and M. G. von Herrath, Selective Immunotherapy of IDDM: A Discussion Based on New Findings from the RIP-LCMV Model for Autoimmune Diabetes," *Transplantation Proceedings* 30:4115-4121, 1998. Applicant respectfully submits that these articles illustrate that those of skill in the art would understand that the illustrations of the invention utilizing these two well-known and accepted animals models are predictive of outcomes in humans.

Applicant submitted as Exhibit A attached to the Response filed herein on December 28, 2000, a Declaration under 37 C.F.R. § 1.132 (resubmitted herewith as Exhibit B to this Preliminary Amendment) describing experiments performed since the filing date of the present application which illustrate the efficacy of the invention method for treating or preventing diabetes in non-obese diabetic (*nod*) mice, an animal model for spontaneous autoimmune diabetes that is generally accepted as reasonably predictive of outcomes in humans. As described in the Declaration, in the first experiment, tests were conducted to determine the effect of induced peripheral expression of self-antigen (porcine insulin B chain) (InsB) on spontaneous occurrence of IDDM in *nod* mice in which diabetes occurs spontaneously in 80% of the females and 30% of the males by 30 weeks of age. The mice were administered intramuscularly a plasmid engineered to express porcine insulin B chain DNA under the control of the initial-early promoter of CMV at the age of 7 days, with boosting at 4 and 8 weeks. Only around 35% of the treated mice displayed full-blown disease in contrast with the expected rate of 80% in naïve female *nod* mice.

As further described in the Exhibit B Declaration, intramuscular administration of the plasmid to *nod*-mice resulted in long-lasting expansion of *both GAD and InsB-specific T cell*

pool committed toward IL-4, but not IFN-γ production (Fig. 2), as shown in the spleens of diabetes-free 30-weeks old treated mice. Thus, a regulatory immune response resulted in treated mice for an epitope (i.e., GAD) that is associated in humans with autoimmune diabetes, but was not included in the plasmid administered.

In addition, an ELISA-based analysis of the effect upon the autoreactive T cell repertoire in mice administered the InsB-containing plasmid that did not develop diabetes by 30 weeks of age showed (Table 2 of Declaration) increased production of IL-4 and TGF-β1 by infiltrating T cells as compared to naïve or control plasmid-inoculated mice. Furthermore, the infiltrating T cells from pInsB-vaccinated mice displayed reduced production of IL-1β. According to the Declaration of Dr. von Herrath, this cytokine profile indicates that in protected mice that were treated according to invention methods a modified autoreactive T cell profile was triggered consisting in a shift from Th1 to Th2 immunity, a positive regulatory immune response.

In yet another experiment described in the Declaration of Dr. von Herrath, *nod* mice were immunized intramuscularly with a control plasmid (100μg/dose of pCMV control) or with a mixture of two plasmids (50μg pCMV-InsB and 50μg pHTLV-IL-4, expressing insulin B and IL-4 cytokine, as described above. Only about 20% of the nod mice treated by inoculation with polynucleotides encoding Ins-B and IL-4 developed symptoms of diabetes by age 18 weeks as compared with over 45% of the control mice.

Thus, Applicant has presented examples from two distinct models of the treatment of autoimmune diabetes using invention methods: a transgenic model contained in the Examples of the original Specification and a spontaneous model of autoimmune diabetes in the nod mouse. Applicant respectfully submits that the results of these experiments confirm that the teachings in the Specification are sufficient to enable those of skill in the art to make and use the invention.

In the Advisory Action (Paper No. 14), the Examiner raised a number of concerns regarding Applicant's interpretation of the results of the experiments described in the Exhibit B Declaration. For example, the Examiner questioned the meaning of the term "% diabetes" as applied to the ordinate (not the abscissa) of the graph shown in Figure 1 attached to the Exhibit B Declaration (Advisory Action, page 2). Applicants respectfully submit that the meaning of the

term is "% of mice that developed symptoms of diabetes"; as would be clear to those of skill in the art in the context of the discussion of the Figure in the Exhibit B Declaration.

In addition, in the Advisory Action, the Examiner questioned the reason that the data for the "controls" were not the same for GAD and InsB since the cells used were the same (Advisory Action, page 2). The answer to this question is that the cells have distinct specificities leading to a polyclonal T cell population. For example, there is no reason to suppose that the cells would have the same number of epitopes for InsB as for GAD. Thus, there is no reason to expect the "controls" to be the same for GAD and Ins-B.

Applicant traverses the Examiner's assertion with regard to the data in Table 2 of the Exhibit B Declaration that:

> ...the data shows that only IL-4 provided any benefit in the claimed method. The other cytokines tested either showed no clear effect or they had a negative effect. ... Specifically, the data showed that an increase in INF-γ was associated with onset of type-I diabetes.

(Advisory Action, page 3). Applicant respectfully submits that, as described in the Exhibit B Declaration, the measured cytokines are those produced by pancreas infiltrating cells, not amounts of cytokine produced by vectors administered to the mice treated. Thus, the noted increase in levels of INF-γ do not reflect on the ability of the cytokines to induce or suppress the symptoms of autoimmune diabetes.

To further address the Examiner's concern raised in the Advisory Action that "only IL-4 would provide any benefit in the claimed method," Applicant submits herewith an unexecuted Supplementary Declaration under 37 C.F.R. § 1.132 by the inventor, Dr. VonHerrath (attached hereto as Exhibit C). A signed copy of the Supplementary Declaration will be submitted as soon as it is received. The Supplemental Declaration describes an additional experiment conducted in which *nod* female mice were injected with invention plasmids containing Ins B chain or with a combination of plasmids expressing Ins B and either IL-10 or IL-4. The results of these tests summarized in Figure 1 attached to the Supplemental Declaration (Exhibit C) show that the combination of Ins B and IL-10 transiently expressed in the treated mice was even more effective at reducing the percent cumulative rate of disease in immunized mice as measured by

blood glucose levels in the treated mice than the combination of Ins B and IL-4. Therefore, Applicant respectfully submits that the Examiner's assertion that IL-4 is the "only" biological response modifier that would be effective in practice of the invention methods is without merit.

Based upon the amendments, the above remarks, the Declaration filed on December 28, 2000 (Exhibit B), and the Supplemental Declaration submitted herewith (Exhibit C), Applicant submits that the present Specification provides sufficient objective data to fully enable the subject matter of claims 1-3, 5, 6, 8, 9-12, 14, 15, 17, 19-22, 24, 27, and 29-39 as presented in this Preliminary Amendment. Therefore, reconsideration and withdrawal of the present rejection for lack of enablement are respectfully requested.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Applicant respectfully traverses the rejection of claims 6-8, 17-21, 27-29, 30 and 36 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. With regard to the Examiner's assertion that the term "biological response modifier" in claims 6, 17 and 27 is allegedly "not an art recognized term and no definition is provided in the claims and specification " (Office Action, page 5), Applicant respectfully submits that the Specification provides a general functional description of the term as used in the claims at issue. The Specification teaches that biological response modifiers (BRMs) are a variety of "immunopotentiating agents" that stimulate the immune system without specificity (Specification, page 26, lines 24-25), including "agents that may not be immunogenic to the host, but nevertheless potentiate immunity by activating or enhancing the activity of cells of the immune system" (Specification, page 27, lines 25- 26). Since the Specification provides a general functional description of the term, Applicants disagree with the Examiner's assertion that the term is defined in the Specification only by a "few examples."

However, to expedite prosecution and reduce the issues, the term "biological response modifier" in claim 1 has been replaced by the phrase "a compound selected from the group consisting of a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and combinations thereof," thus removing the grounds for the rejection.

With regard to claim 9, the Examiner asserts that there is insufficient antecedent basis for the terms "nucleic acid construct" in line 2 and "biological response modifier" in line 3. However, Applicant respectfully submits that claim 9 depends from claim 1, which recites the term "a nucleic acid construct, " thus providing proper antecedent basis for the term "*the* nucleic acid construct" in dependent claim 9. In addition, both claim 1 and claim 9 have been amended to replace "biological response modifier by the term "compound." Accordingly, the recitations of "a compound" in claim 1 provides proper antecedent basis for the term "*the* compound" in dependent claim 9.

With regard to claim 20, the Examiner alleges a lack of antecedent basis for the term "biological response modifier" in line 3. However, claim 20 has been amended to replace the term "biological response modifier" by the term "compound". Applicants submit that amended claim 20 depends from amended claim 17, which recites the term "a compound," thus providing proper antecedent basis for the term "the compound" in line 3 of dependent claim 20.

With regard to claim 29, the Examiner alleges a lack of antecedent basis for the term "biological response modifier" in line 1 thereof. However, Applicants submit that the term "biological response modifier" has been replaced by the term "compound" in amended claim 29, which depends from amended claim 27. Amended claim 27 provides proper antecedent basis for the term "*the* compound" in claim 29, from which it depends.

With regard to the rejection of claim 30 as allegedly being indefinite due to use of the phrase "regulatory element," claim 30 has been amended herein to further define the meaning of the term "regulatory element" by reciting that the regulatory element is "operatively linked to nucleic acid encoding the at least one epitope or the biological response modifier and/or the biological response modifier." Thus, as amended by this communication, the language of claim 30 is definite and parallels that of claims 9 and 20, which were not included in the present rejection.

Applicant respectfully traverses the Examiner's assertion that the term "non-pathogenic ... Th lymphocytes" renders claim 36 indefinite because the term is allegedly "not an art recognized term" (Office Action, page 7). Applicants respectfully submit that, in amended claim 36, the phrase at issue has been replaced so as to avoid any alleged indefiniteness by

reciting: "modification of the immune response comprises increase in autoreactive T cells specific for at least one antigen associated with autoimmune diabetes whose epitope is not expressed by the plasmid."

In view of the above amendments and arguments, Applicant respectfully submits that amended claims 6-8, 17-21, 27-29, 30 and 36 meet all requirements under 35 U.S.C. § 112, Second Paragraph.

The Rejection under 35 U.S.C. § 102

Applicant's invention immunomodulating composition for use in treating or preventing diabetes, as defined by present claim 1, distinguishes over the disclosure of each of the allegedly anticipating references cited by comprising a nucleic acid construct encoding at least one epitope from a self-antigen and a compound selected from the group consisting of a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and combinations thereof, in a pharmaceutically acceptable carrier.

Applicant's invention method for modifying an ongoing immune response in a subject against a self-antigen associated with autoimmune diabetes, as defined by amended claim 11, distinguishes over each of the allegedly anticipating references by requiring administering to the subject by peripheral injection an immunomodulatory effective amount of a plasmid expressing a nucleic acid construct encoding at least one epitope from a self-antigen associated with autoimmune diabetes in a pharmaceutically acceptable carrier. Transient expression of the epitope in the subject results in a positive regulatory immune response to multiple self-antigens associated with the autoimmune diabetes.

Applicant's invention method for controlling the blood glucose level in a subject having an ongoing immune response against a self-antigen associated with autoimmune diabetes, as defined by amended claim 22, distinguishes over each of the allegedly anticipating references by requiring administering to the subject by peripheral injection, an immunomodulatory effective amount of a plasmid expressing a nucleic acid construct encoding at least one epitope from a self-antigen associated with autoimmune diabetes in a pharmaceutically acceptable carrier. Expression of the epitope in the subject results in a positive regulatory immune response against

multiple self-antigens associated with the autoimmune diabetes so as to control the blood glucose level of the subject.

Thus, Applicant's invention, as defined by amended claims 1, 11 and 22, pertains to modulation of an ongoing immune response in a subject against a self-antigen associated with autoimmune diabetes by administering a nucleic acid construct to the subject so as to result in a "positive regulatory" immune response (e.g., a Th2 response), thereby controlling the blood glucose level of the subject. Applicant defines a "self-antigen epitope" as follows:

> ... a peptide or protein against which an immune response can be elicited. The self-antigen epitope(s) is an immunogenic peptide protein fragment or protein derived from an autoreactive antigen or a cell involved in autoimmune disease. The immune response directed against the epitope or protein will protect the individual against the specific infection or disease with which the self-antigen epitope(s) is associated.

(Specification, page 12, lines 26-31). In addition, as is well understood in the art, each autoimmune disease is characterized by an immune response in the host directed at one or more "self antigens"; whereas in the absence of autoimmune disease there are no active immune responses to self antigens, and no symptoms appear (See, WO 97/46253, page 17, of record herein).

A. The Liu Reference

Applicants respectfully traverse the rejection of claims 1, 2, 5, 9-11, 13, 14, 16, 20-24, 26 and 30-36 under 35 U.S.C. § 102(a) for allegedly being anticipated by Jingxue Liu et al. (*Gene Ther Mol Biol* 3:197-206, 1998; hereinafter "Liu"). Liu fails to disclose an immunomodulary composition as required by amended claim 1. In contrast to Applicant's immunomodulating compositions, Liu discloses a nucleic acid construct encoding a truncated version of human glutamic acid decarboxylase 65 (GAD65) and the leader peptide (i.e., the first 23 amino acids) of IL-2 (See Liu, Materials and Methods, page 203). The function of the IL-2 leader peptide in the prior art construct is to cause secretion by mammalian cells of normally intracellular proteins (See Liu, page 198, Col 2). Liu fails to disclose that the IL-2 leader peptide possesses the cytokine function of IL-2 and, indeed, it does not. Thus Applicant respectfully submits that Liu

fails to disclose a nucleic acid construct encoding both an epitope of a self-antigen and a compound selected from the group consisting of a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and combinations thereof, in a pharmaceutically acceptable carrier.

Applicant respectfully disagrees with the Examiner's conclusion that Liu's disclosure anticipates the invention composition of amended claim 1 or the invention methods of claims 11 and 22 (and all claims dependent thereon) because Lie allegedly discloses induction of antibodies to GAD. Liu administered GAD-expressing CMV plasmids to *nod* mice and observed a reduction in insulitis. Liu is completely silent regarding whether the disclosed method resulted control of blood glucose levels in the treated mice. Moreover, Applicant respectfully submits that Liu's finding of a reduction in insulitis associated with induction of antibodies does not anticipate or predict the present invention, hich involves induction of regulatory cells that modulate an ongoing immune response to a self-antigen associated with autoimmune diabetes so as to control (i.e. suppress or prevent increase in blood glucose levels in the treated individual.

Indeed, rather than whole antibody titers, as the Examiner implies, it is the resulting antibody *isotype profile* that is significant in the invention methods. For example, an antibody profile that includes substantial presence of IgG1 and IgG3 (associated with Th2) reflects the T cell profile referred to in the present claims as "a positive regulatory immune response." Substantial presence of other antibody isotypes, such as IgG2a and IgG2b, are associated with non-Th2 responses. Liu is absolutely silent regarding the induction of immune response with a particular profile indicative of a "positive regulatory immune response, as the term is used in Applicant's claims and as is understood in the art. Therefore, Applicant respectfully submits that Liu's disclosure regarding induction of antibodies cannot be extrapolated as an indication of induction of a positive regulatory immune response.

In view of the above amendments and remarks, Applicant respectfully submits that Liu does not anticipate the invention constructs and methods, as defined by amended claims 1-3, 5, 7-14, 16-24 and 26-38, under 35 U.S.C. § 102(a).

In addition, Applicant respectfully submits that Liu fails to suggest under 35 U.S.C. § 103 the invention nucleic acid construct encoding the combination of an epitope of a self-antigen and "a compound selected from the group consisting of a cytokine, a chemokine, an interferon,

ligands for lymphocyte receptors, and combinations thereof, as is required by amended claim 1. These compounds are natural mediators that act on lymphocytes by engaging receptors different from antigen-specific receptors. In Liu's nucleic acid construct the IL-2 derived sequence is only a "leader peptide" whose function normally is to facilitate passage through a membrane, such as insertion into membranes of the endoplasmic reticulum, as is known in the art (See for example, Lewin et al., *genes VII,* Oxford University Press, New York, 2000, Glossary). Liu fails to suggest any modification of the GAD65 containing construct to include nucleic acid that encodes a compound that will effect a positive immune response in the subject having an ongoing immune response to an antigen associated with autoimmune diabetes, such as type I diabetes. Thus, Applicant respectfully submits that Liu would also fail to suggest Applicant's compositions under 35 USC § 103.

The deficiencies of Liu for anticipating Applicant's invention methods apply as well to the analysis of the invention methods for alleged unpatentability under 35 USC § 103. In addition, Applicant respectfully submits that, at best, Liu's disclosure is an invitation to try the approach of testing the effect of intramuscular immunization of naked DNA in the *nod* mouse model for the purpose of treating autoimmune diabetes via gene therapy, i.e., wherein the therapeutic or preventative effect depends upon sustained expression of the construct. For example, Liu concludes that "injection of DNA encoding [GAD65] ... suggest[s] the possibility that this form of gene therapy might be useful to prevent clinical manifestation of IDDM" (Liu, page 198, Col. 2). Liu contains no suggestion whatsoever that the prior art construct could be administered by peripheral injection for transient expression *in a plasmid* to trigger a "positive regulatory immune response to multiple self-antigens associated with the autoimmune diabetes, as required by amended claim 11, or to control the blood glucose level of the subject, as required by amended claim 22.

Accordingly, Applicant respectfully submits that the methods of amended claims 11, 12, 14, 15, 17, 19-22, 24, 27, and 29-39 are not *prima facie* obvious in view of Liu.

B. WO 97/46253

Applicant respectfully traverses the rejection of claims 1-9, 11-20, 22-30 and 32-36 under 35 U.S.C. § 102(b) for allegedly being anticipated by WO 97/46253; hereinafter "'253"). Applicant disagrees with the Examiner's assertion that the present claims are anticipated by the following passage of '253:

> At pages 22, lines 22-25 WO97/46253 recites "[a]ncillary nucleic acid sequences coding for peptides known to stimulate, modify, or modulate a host's immune response, can be coadministered with the above-described antigens. Thus, genes encoding one or [sic] more of the various cytokines ..."

(Office Action page 9). In fact, '253 discloses constructs suitable for treatment of rheumatoid arthritis and multiple sclerosis, but is absolutely silent regarding whether such DNA vaccines might modulate an ongoing immune response to self-antigen associated with autoimmune diabetes. In addition, by virtue of the indiscriminate recommendation that nucleic acid sequences encoding any peptide that stimulates, modifies or modulates a host's immune response would be suitable for inclusion in the prior art DNA vaccine, '253 fails to disclose selection of a suitable compound for use in combination with a self-antigen that "results in a positive regulatory immune response to multiple self-antigens associated with autoimmune diabetes" or would "control the subject's level of blood glucose." Thus, Applicant respectfully submits that '253 fails to disclose key elements of Applicant's compositions and methods, which all require that the autoimmune condition treated or prevented is "autoimmune diabetes" and that the compound administered along with the self-antigen, if any, is a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, or a combinations thereof, particularly IL-4 or IL-10. Accordingly, Applicant submits that '253 fails to disclose each and every element of amended claims 1-3, 5, 6, 8, 9-12, 14, 15, 17, 19-22, 24, 27, and 29-39 as would be required to constitute anticipation under 35 U.S.C. § 102(a).

In addition, Applicant respectfully submits that '253 fails to suggest the invention constructs and methods under 35 U.S.C. § 103(a). '253 discloses treatment of multiple sclerosis, but is completely silent regarding modulation of immune responses associated with autoimmune diabetes. Accordingly, '253 provides no motivation to make or use a composition suitable for

causing transient transfection of at least one epitope of a self-antigen associated with autoimmune diabetes to effect a positive regulatory immune response to multiple self-antigens associated with the autoimmune diabetes, as required by amended claim 11, or to control the blood glucose level of the subject, as required by amended claim 22. In addition, there is no suggestion in '253 how to modify the disclosed constructs and methods to achieve such goals.

Autoimmune diseases differ considerably from each other, and other autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis, differ considerably from autoimmune diabetes . Hence those of skill in the art understand that disclosure regarding other types of autoimmune disease cannot reasonably be extrapolated to pertain to treatment or prevention of autoimmune diabetes. For example, rheumatoid arthritis and multiple sclerosis affect categories of individuals with different genetic backgrounds than those who develop autoimmune diabetes. In addition, clinical trials have shown that non-overlapping categories of therapeutics may be effective against the inflammatory processes associated with these diseases. Preclinical models showed that whereas inhibition of co-stimulation suppresses inflammation associated with multiple sclerosis, it has an aggravating effect on evolution of diabetes (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10795741&dopt=Abstract; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10605004&dopt=Abstract). In addition, antibodies as well as T-cells are thought to be involved in multiple sclerosis; whereas antibodies do not play a pathogeneic role in autoimmune diabetes.

Yet, '253 is silent regarding such considerations. Therefore, Applicant respectfully submits '253 fails to suggest to those of skill in the art how to pick and choose among the disclosure of the reference to arrive at a construct and method of its use that would be beneficial with respect to autoimmune diabetes.

Accordingly, Applicant submits that the '253 reference fails to disclose each and every element of the present claims, as would be required to establish anticipation under 35 U.S.C.§ 102, and also fails to suggest the subject matter of the present invention so as to render the present claims *prima facie* obvious under 35 U.S.C.§ 103.

C. WO 95/21926

Applicant respectfully traverses the rejection of claims 1, 4, 11, 12, 15, 16, 22, 25, 26 30 and 32-36 and 30 under 35 U.S.C. § 102(b), for allegedly being anticipated by WO 95/21926 (hereinafter "'926").

By contrast to Applicant's invention as described above, '926 fails to disclose a nucleic acid sequence encoding both a compound selected from a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and combinations thereof, and an epitope of a "self-antigen" as the term is understood in the art and as used in the Specification and claims herein. Instead, '926 discloses that a sequence encoding a" tolerogenic" epitope is to be placed at the N-terminus variable region of an immunoglobulin-encoding sequence. Applicants respectfully submit that an "immunoglobulin" as the term is used by '926 is not a "a cytokine, a chemokine, an interferon, or a ligand for a lymphocyte receptor" as the term is used in Applicants' specification and claims and as understood by those of skill in the art. Rather an immunoglobulin is an antibody or a γ globulin. Thus, '926 fails to disclose each and every element of Applicants' constructs as defined by amended claims 1. In addition, '926 is silent regarding modification of an ongoing immune response to a self-antigen associated with autoimmune diabetes so as to result in a positive regulatory immune response to multiple self-antigens associated with autoimmune diabetes or so as to result in control of a subject's blood glucose level, as would be required for anticipation of claims 11 and 22 under 35 U.S.C. § 102(a).

In addition, Applicants respectfully submit that '926 fails to provide any motivation or suggestion to those of skill in the art how to modify of the disclosed construct to arrive at the invention construct and treatment methods. As the Examiner acknowledges, the disclosure of '926 pertains to a plasmid vector expressing myelin basic protein that is used in treatment of multiple sclerosis. '926 is completely silent regarding constructs useful for modifying an ongoing immune response to a self-antigen associated with autoimmune diabetes in a subject, such as a human. In addition, '926 teaches that the prior art construct is expressed in a host cell and the expressed protein is administered to the animal's circulation as a fusion protein; whereas Applicant's composition is formulated in a plasmid for peripheral administration to the subject

and for transient expression of the epitope by the subject (e.g. as a DNA vaccine). Hence, there is no suggestion in '926 to modify the prior art constructs and methods to arrive at Applicant's invention. Accordingly, Applicant submits that the '926 reference would also fail to suggest the subject matter of the present invention so as to render claims 1, 11 or 22 *prima facie* obvious under 35 U.S.C.§ 103.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Attachments: Exhibit A – Pending claims
Exhibit B - Declaration under 37 C.F.R. § 1.132
Exhibit C - Supplementary Declaration under 37 C.F.R. § 1.132 (unsigned)

EXHIBIT A

Version with Markings to Show Changes Made

In the Specification:

Please delete the title of the Specification and insert the following replacement Specification title: COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF AUTOIMMUNE DIABETES.

In the Claims

1. (Twice Amended) An immunomodulating composition for [use in treating or preventing an autoimmune disorder] modulating an immune response comprising a nucleic acid construct encoding at least one epitope from a self-antigen and a compound selected from the group consisting of a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and combinations thereof, in a pharmaceutically acceptable carrier.

2. (Twice Amended) The composition of claim 1, wherein the immune response is to a self-antigen associated with autoimmune [disorder is selected from the group consisting of multiple sclerosis (MS), rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, scleroderma, myasthenia gravis and ulcerative colitis] diabetes.

3. (Amended) The composition of claim 1, wherein the epitope is derived from insulin B-chain or GAD65.

6. (Amended) The composition of claim 1, further comprising a nucleic acid sequence encoding a [biological response modifier] compound selected from the group consisting of a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and combination thereof.

8. (Twice Amended) The composition of claim 6 wherein the biological response modifier is [selected from the group consisting of IL-l (alpha or beta), IL-2, IL-3,] IL-4, [IL-5, IL-6, IL-7, IL-8, IL-9,] IL-10, [IL-11, IL-12, IL-13, GM-CSF, M-CSF, G-CSF, LIF, LT, TGF-beta, gamma-IFN (or alpha or beta-IFN), TNF-alpha, BCGF, CD2, ICAM and any] or a combination thereof.

9. (Twice Amended) The composition of claim 1, wherein the nucleic acid construct further comprises a regulatory element operatively linked to nucleic acid encoding the at least one epitope or the [biological response modifier] compound.

11. (Twice Amended) A method for [treating or preventing autoimmune disorder] modifying an ongoing immune response in a subject [having or at risk of having the disorder] against a self-antigen associated with autoimmune diabetes comprising administering to the subject by peripheral injection an immunomodulatory effective amount of a plasmid expressing a nucleic acid construct encoding at least one epitope from a self-antigen associated with autoimmune diabetes in a pharmaceutically acceptable carrier, wherein transient expression of the epitope in the subject [generates] results in a positive regulatory immune response[, thereby treating or preventing the disorder] to multiple self-antigens associated with the autoimmune diabetes.

15. (Amended) The method of claim 11, wherein [the epitope is derived from myelin basic protein] the regulatory immune response prevents increase of the blood glucose level of the subject.

17. (Amended) The method of claim 11, further comprising administering to the subject a nucleic acid sequence encoding a [biological response modifier] compound selected from the group consisting of a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and an interleukin.

19. (Twice Amended) The method of claim 17, wherein the [biological response modifier] compound is [selected from the group consisting of IL-l(alpha or beta), IL-2, IL-3,] IL-4, [IL-5,

IL-6, IL-7, IL-8, IL-9,] IL-10, [IL-11, IL-12, IL-13, GM-CSF, M-CSF, G-CSF, LIF, LT, TGF-beta, gamma-IFN (or alpha or beta-IFN), TNF-alpha, BCGF, CD2, ICAM and any] or a combination thereof.

20. (Twice Amended) The method of claim [11] 17, wherein the nucleic acid construct further comprises a regulatory element operatively linked to nucleic acid encoding the at least one epitope or the [biological response modifier] compound.

22. (Twice Amended) A method for [inducing a regulatory immune response] controlling the blood glucose level in a subject having [or at risk of having an autoimmune disorder] an ongoing immune response against a self-antigen associated with autoimmune diabetes comprising administering to the subject by peripheral injection, an immunomodulatory effective amount of a plasmid expressing a nucleic acid construct encoding at least one epitope from a self-antigen associated with autoimmune diabetes in a pharmaceutically acceptable carrier, wherein expression of the epitope in the subject [generates] results in a positive regulatory immune response against multiple self-antigens associated with the autoimmune diabetes so as to control the blood glucose level of the subject.

27. (Amended) The method of claim 22, further comprising administering to the subject a nucleic acid sequence encoding a [biological response modifier] compound selected from the group consisting of a cytokine, a chemokine, an interferon, ligands for lymphocyte receptors, and combinations thereof.

29. (Twice Amended) The method of claim 27, wherein the [biological response modifier] compound is [selected from the group consisting of [IL-l(alpha or beta), IL-2, IL-3,] IL-4, [IL-5, IL-6, IL-7, IL-8, IL-9,] IL-10,[IL-11, IL-12, IL-13, GM-CSF, M-CSF, G-CSF, LIF, LT, TGF-beta, gamma-IFN (or alpha or beta-IFN), TNF-alpha, BCGF, CD2, and ICAM] or a combination thereof.

32. (Amended) The method of claim 11, wherein a single administration of the nucleic acid construct is effective to [treat or prevent the disorder] modify the ongoing immune response.

33. (Amended) The method of claim 22, wherein a single administration of the nucleic acid construct is effective to [induce the regulatory immune response] control the blood glucose of the subject.

34. (Amended) The method of claim 11, wherein the [positive] modification of the immune response [comprises induction of] affects T-cells reactive to [the autoantigen] multiple antigens associated with autoimmune diabetes.

35. (Amended) The method of claim 11, wherein the [positive] modification of the immune response comprises induction of Th2 lymphocytes reactive to the [autoantigen] self-antigen.

36. (Amended) The method of claim 11, wherein the [positive] modification of the immune response comprises [induction of non-pathogenic or suppressor Th lymphocytes reactive to the autoantigen] autoreactive T cells specific for at least one antigen associated with autoimmune diabetes whose epitope is not expressed by the plasmid.

37. (New) The method of claim 19, wherein the self epitope is derived from GAD65.

38. (New) The method of claim 29, wherein the self epitope is derived from GAD65.

39. (New) The method of claim 36, wherein the epitope expressed by the plasmid is derived from insulin B chain and the antigen whose epitope is not expressed by the plasmid is GAD65.